

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH**

SUMMARY OF TOXICOLOGY DATA

AMINOPYRALID

**Chemical Code # 5927, Tolerance # 52992
SB 950 # NA**

May 3, 2006

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect indicated
Chronic toxicity, dog:	No data gap, no adverse effect indicated
Oncogenicity, rat:	No data gap, no adverse effect indicated
Oncogenicity, mouse:	No data gap, no adverse effect indicated
Reproduction, rat:	No data gap, no adverse effect indicated
Teratology, rat:	No data gap, no adverse effect indicated
Teratology, rabbit:	No data gap, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect indicated
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	No data gap, no adverse effect indicated

Toxicology one-liners are attached.

All record numbers through 219980 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T060503

Revised by T. Moore, 5/3/06

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 52992-0040; 219889; "XDE-750: Two-Year Chronic Toxicity/Oncogenicity and Neurotoxicity Study in Fischer 344 Rats"; (K.A. Johnson, M.D. Dryzga; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011049; 3/4/04); Fifty Fischer 344 rats/sex/group received 0, 5, 50, 500 or 1000 mg/kg/day of XDE-750 (lot no. F0031-143; purity: 94.5%) in the diet for 24 months. Another 15 animals/sex/group were treated for 12 months. Fifteen animals/sex/group were allocated to an interim group on study for 12 months. Ten of the animals were used for an interim assessment in the chronic toxicity study. Five of these animals/sex/group plus five additional animals/sex/group were selected to examine neurotoxic effects through 12 months as well. The mean body weight of both sexes in the 1000 mg/kg group and the males in the 500 mg/kg group were less than that of the controls over the course of the study. There was no apparent treatment-related effect upon food consumption. Although the prothrombin time demonstrated statistically significant differences at various times during the study, there was no consistent dose-related response. The clinical chemistry and ophthalmology data did not reveal any treatment-related effects. In the urinalysis, the urine volumes demonstrated a dose-related increase for both sexes in the 500 and 1000 mg/kg groups ($p < 0.05$) and a dose-related decrease in specific gravity for both sexes in these two groups. The urine pH of both sexes in these two groups was consistently less than that of the control animals throughout the study. However, no lesions were evident in the kidneys of these animals. The mean absolute and relative weights of the full cecum and the empty cecum of both sexes in the 500 and 1000 mg/kg groups were greater than those values of the control group ($p < 0.05$) at both 12 and 24 months. These results corresponded to the gross pathology in which the cecum was described as increased in size for both sexes in the 500 and 1000 mg/kg groups at both time points. In the histopathology, an increased incidence of very slight diffuse mucosal hyperplasia was noted in the cecums of both sexes in the 1000 mg/kg group at both 12 and 24 months (12 months, (M) 0: 0/10 vs. 1000: 8/10, (F) 0: 0/10 vs. 1000: 7/10, 24 months, (M) 0: 3/50 vs. 1000: 12/50 ($p < 0.05$), (F) 0: 3/50 vs. 1000: 8/50). Treatment also resulted in a decrease of spermatid elements in the epididymides of the 1000 mg/kg males at 24 months. **No adverse effect indicated. Chronic Dietary Toxicity NOEL:** (M/F) 50 mg/kg/day (based upon the treatment-related increase in the absolute and relative cecal weights of both sexes in the 500 mg/kg group); **no evidence of carcinogenicity was apparent. Study acceptable.** (Moore, 1/25/06)

CHRONIC TOXICITY, RAT

See Combined Rat, above.

CHRONIC TOXICITY, DOG

** 52992-0052; 219938; "XDE-750: One-Year Dietary Toxicity Study in Beagle Dogs"; (K.E. Stebbins, S.J. Day; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 021027; 9/10/03); Four beagle dogs/sex/group received 0, 300, 3000 or 30000 ppm of XDE-750 (lot no. F-0031-143, purity: 94.5%) in the diet for 52 weeks ((M) 0, 9.9, 99.2, 967 mg/kg/day, (F) 0, 9.2, 93.2, 1038 mg/kg/day). There was no apparent treatment-related effect evident in the mean body weight and food consumption data. The ophthalmology, hematology, clinical chemistry and urinalysis evaluations did not indicate any treatment-related effects. The mean relative liver weights of both sexes in the 30000 ppm group were greater than those of the controls ($p < 0.05$). Very slight centrilobular hepatocytic hypertrophy was noted in the livers of two females and two males of the 30000 ppm group. In the stomach, slight hyperplasia of the mucosal lymphoid tissue was evident for 3 males and 4 females of the 30000 ppm group. In addition, slight hyperplasia and hypertrophy of the mucosal tissue and very slight to slight chronic diffuse inflammation of the mucosa in the stomach were noted for all of the animals in the 30000 ppm group. **No adverse effect indicated. Chronic Dietary NOEL:** (M/F) 3000 ppm ((M) 99.2 mg/kg/day; (F) 93.2 mg/kg/day) (based upon the incidence of mucosal hyperplasia in the stomach and hepatocytic hyperplasia in the liver of the 30000 ppm group animals); **Study acceptable.** (Moore, 2/1/06)

ONCOGENICITY, RAT

See Combined Rat, above.

ONCOGENICITY, MOUSE

** 52992-0053; 219939; "XDE-750: Oncogenicity Dietary Study in CD-1 Mice"; (K.E. Stebbins, S.J. Day; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011163; 12/19/03); Fifty CD-1 mice/sex/group received 0, 50, 250 or 1000 mg/kg/day of XDE-750 (lot no. F0031-143; purity: 94.5%) in the diet for 18 months. There was no apparent treatment-related effect upon the mortality, mean body weight gain or food consumption of the treated animals. The total white blood cell count and differential white blood cell count did not indicate any treatment-related effect. There was no treatment-related effect indicated by the ophthalmological examination. The necropsy examination did not reveal any treatment-related lesions or effect on organ weights. There were no treatment-related lesions evident in the histopathological examination. **No adverse effect was evident. Chronic Dietary NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of any treatment-related effects at the highest dose tested); **No oncogenicity evident.. Study acceptable.** (Moore, 2/2/06)

REPRODUCTION, RAT

** 52992-0060; 219966; "XDE-750: Two-Generation Dietary Reproduction Toxicity Study in CD Rats"; (M.S. Marty, C.L. Zablony, J. Thomas; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 01125; 6/16/03); CD rats/sex/group received with 0, 50, 250 or 1000 mg/kg/day of XDE-750 (lot no. F0031-143; purity: 94.5%) in the diet for two generations. Thirty rats/sex/group in both the P1 and P2 generations were treated for 10 weeks prior to mating, during mating, and the 3 weeks of gestation and 3 weeks of lactation. The P2 generation was derived from the F1 offspring at the time of weaning. The P1 and P2 parental generations did not demonstrate any treatment-related effects upon mean body weight or food consumption. In the necropsy examination, the mean absolute and relative cecum weights (both full and empty) were increased for both sexes in both generations of the 1000 mg/kg group and for the males in the P2 generation of the 250 mg/kg group ($p < 0.05$). For the P1 generation, absolute and relative weights for the full cecum and the relative weight for the empty cecum were increased for both sexes of the 250 mg/kg group ($p < 0.05$). The gross pathological examination of this tissue indicated the incidence of enlarged cecums in the 250 and 1000 mg/kg groups (P1 generation: (M) 0: 0/29 vs. 1000: 21/30, (F) 0: 0/30 vs. 250: 2/30, 1000: 20/29, P2 generation: (M) 0: 0/30 vs. 250: 2/29, 1000: 17/30, (F) 0: 0/30 vs. 250: 4/30, 1000: 10/30). There were no treatment-related effects upon the reproductive parameters or the development of the offspring of either generation. **No adverse effect indicated. Parental NOEL:** (M/F) 50 mg/kg/day (based upon the increased mean absolute and relative cecum weights (full and empty) of the 250 mg/kg parents); **Reproduction NOEL:** 1000 mg/kg/day (based upon the lack of treatment-related effects at the highest dose tested); **Developmental NOEL:** 1000 mg/kg/day (based upon the lack of treatment-related effects at the highest dose tested); **Study acceptable.** (Moore, 2/15/06)

TERATOLOGY, RAT

** 52992-0054; 219956; "XDE-750: Oral Gavage Developmental Toxicity Study in CD Rats"; (E.W. Carney, B. Tornesi; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011061; 11/20/01); Twenty five time-mated female CD rats/group were dosed orally by gavage with 0, 100, 300, or 1000 mg/kg/day of XDE-750 (lot no. F0031-143; purity: 94.5%) from day 6 through day 20 of gestation. The vehicle was aqueous 0.5% Methocel A4M. There was no treatment-related effect upon the dams' mean body weight gain or food consumption. Fetal development was not affected by the treatment. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (based upon the lack of treatment-related effects on the highest dose tested); **Developmental NOEL:** 1000 mg/kg/day (based upon the lack of treatment-related effects on the highest dose tested); **Study acceptable.** (Moore, 2/3/06)
** 52992-0056; 219958; "GF-871: An Oral Developmental Toxicity Study in Sprague-Dawley Rats"; (B.A. Thorsrud; Charles River Laboratories, Inc., Discovery and Development Services, Ohio Division, Spencerville, OH; Study No. 3504.344; 3/12/04); Twenty five time-mated female

Sprague-Dawley rats/group were dosed orally by gavage with 0, 200, 500 or 1000 mg/kg/day of GF-871 (lot no. 173-162-1A, a.i.: 41.3%) (based on the concentration of the active ingredient (XDE-750 TIPA)) from day 6 through day 20 of gestation. The equivalent concentration of the formulation was 484, 1211, and 2421 mg/kg/day of GF-871. There were no treatment-related effects upon the dams. The treatment did not affect the development of the fetuses. **No adverse effect indicated. Maternal NOEL:** 1000 mg/kg/day (XDE-750 TIPA) (based upon the lack of treatment-related effects on the dams at the highest dosing level); **Developmental NOEL:** 1000 mg/kg/day (XDE-750 TIPA) (based upon the lack of treatment-related effects on the fetuses at the highest dosing level); **Study acceptable.** (Moore, 2/8/06)

Range-finding Teratology Studies

52992-0058; 219960; "XDE-750: Developmental Toxicity Probe Study in CD Rats"; (B. Tornesi, E.W. Carney, J. Thomas; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 001234; 5/4/01); Eight time-mated female CD rats/group were dosed orally by gavage with 0, 250, 500, 750 or 1000 mg/kg of XDE-750 (lot no. F0031-143; purity: 94.5%) from day 6 through day 20 of gestation. There were no treatment-related effects upon the dams. The development of the fetuses was not affected by the treatment. These data were used to establish the dose range for the guideline rat teratology study. **No adverse effect indicated. Study supplemental.** (Moore, 2/9/06)

TERATOLOGY, RABBIT

** 52992-0055; 219957; "XDE-750: Oral Gavage Developmental Toxicity Study in New Zealand White Rabbits"; (M.S. Marty, A.B. Liberacki, J. Thomas; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011047, 011047A; 3/13/02); In Phase I, 26 time-mated female New Zealand White rabbits/group were dosed orally by gavage with 0, 25, 100 or 250 mg/kg/day of XDE-750 (lot no. F0031-143; purity: 94.5%) from day 7 through day 27 of gestation (vehicle: aqueous 0.5% METHOCEL A4M). There were no treatment-related effects upon the does in the highest group tested so a phase II was implemented in which 26 time-mated females/group were dosed in the same manner with 0, 500 or 750 mg/kg/day with the test material from day 7 through day 27 of gestation as well. In this second phase, the 750 mg/kg does demonstrated such severe clinical signs that the maximum tolerated dose was considered to have been exceeded so the surviving animals in this group were all euthanized by day 19 of gestation. In the 500 mg/kg group, twenty three of the animals exhibited an incoordinated gait during the treatment period and a mean body weight loss and lower food consumption at the time dosing was initiated. There was no treatment-related effect upon the fetal development at the highest dose for which data was available, 500 mg/kg. **No adverse effect indicated. Maternal NOEL:** 250 mg/kg/day (based upon mean body weight loss for the 1st 3 days after dosing initiation and the incidence of incoordinated gait of the does in the 500 mg/kg group); **Developmental NOEL:** 500 mg/kg/day (based upon the lack of treatment-related effects on the fetuses at the highest dose for which data was available); **Study acceptable.** (Moore, 2/7/06)

** 52992-0057; 219959; "GF-871: Oral Gavage Developmental Toxicity Study in New Zealand White Rabbits"; (E.W. Carney, B. Tornesi; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 031142; 3/5/06); Twenty six time-mated female New Zealand White rabbits/group were dosed orally by gavage with 0, 200, 500 or 1000 mg/kg/day of GF-871 (lot no. 173-162-1A; a.i.: 41.3%) (doses based on the concentration of the active ingredient (XDE-750 TIPA)) from day 7 through day 28 of gestation. The equivalent concentration of the formulation was 484, 1211, and 2421 mg/kg/day of GF-871. Three does in the 1000 mg/kg group and one doe in the 500 mg/kg group were euthanized between gestation days 14 and 18 because of severe body weight loss. One, 2 and 19 animals in the 200, 500 and 1000 mg/kg groups, respectively, demonstrated an abnormal gait at sometime during the study. The mean body weight and food consumption of the 1000 mg/kg does were less than those of the control throughout the study. The mean body weight of the fetuses in the 1000 mg/kg group was less than that of the control ($p < 0.05$). There were no other treatment-related effects upon the fetuses. **No adverse effect indicated. Maternal NOEL:** <200 mg/kg/day (XDE-750 TIPA) (based upon the clinical symptom of incoordinated gait noted for a doe in the 200 mg/kg group);

Developmental NOEL: 500 mg/kg/day (XDE-750 TIPA) (based upon the lower mean body weight of the fetuses in the 1000 mg/kg group); **Study acceptable.** (Moore, 2/9/06)

Range-finding Teratology Studies

52992-0059; 219961; "XDE-750: Oral Gavage Developmental Toxicity Probe Study in New Zealand White Rabbits"; (A.B. Liberacki, M.S. Marty, J. Thomas; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 001235; 5/2/01); Seven time-mated female New Zealand White rabbits/group were dosed orally by gavage with 0, 250, 500, 750 or 1000 mg/kg/day of 0, 25, 100 or 250 mg/kg/day of XDE-750 (lot no. F0031-143; purity: 94.5%) from day 7 through day 27 of gestation (vehicle: aqueous 0.5% METHOCEL A4M). Early in the dosing regimen, the does in the 750 and 1000 mg/kg treatment groups demonstrated lower mean food consumption and body weight gain, resulting in the termination of their treatment on gestation days 17 and 10, respectively. Erosions and ulcers were noted in the stomachs of these animals. The 250 and 500 mg/kg animals also suffered reduced body weight gain and food consumption as a consequence of the dosing regimen. The mean absolute and relative liver weights of the 500 mg/kg does were less than those values for the controls ($p < 0.05$). No effect on fetal development was noted. **No adverse effect was indicated.** These data were used to establish the dose range for the guideline rabbit teratology study. **Study supplemental.** (Moore, 2/9/06)

GENE MUTATION

** 52992-0061; 219967; "*Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with XDE-750"; (M.S. Mecchi; Covance Laboratories, Inc., Vienna, VA; Study No. 22338-0-422OECD; 10/16/01, amended, 11/8/01); *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2uvrA were preincubated for 20 ± 2 minutes followed by treatment for 52 ± 4 hours at 37° C with XDE-750 (lot no. F0031-143, purity: 94.5%) at concentrations ranging from 100 to 5000 ug/plate with and without S9 activation. All treatment levels of the test article, the vehicle controls and the positive controls were plated in triplicate in two trials. Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. The test material did not produce an increase in the number of revertants per plate of any of the test strains either in the presence or absence of microsomal activation. The positive controls were functional. **No adverse effects. Study acceptable** (Moore, 2/15/06).

** 52992-0062; 219968; "*Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay Preincubation Method with a Confirmatory Assay with GF-871"; (M.S. Mecchi; Covance Laboratories, Inc., Vienna, VA; Study No. 25552-0-422OECD; 3/2/04); *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP2uvrA were preincubated for 20 ± 2 minutes followed by treatment for 52 ± 4 hours at 37° C with GF-871 (XDE-750 TIPA) (lot no. 173-162-1A; a.i.: 41.3%) at concentrations ranging from 33.3 to 5000 ug/plate (XDE-750 TIPA) with and without S9 activation. All treatment levels of the test article, the vehicle controls and the positive controls were plated in triplicate in two trials. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. The test material did not produce an increase in the number of revertants per plate of any of the test strains either in the presence or absence of microsomal activation. The positive controls were functional. **No adverse effects. Study acceptable** (Moore, 2/16/06).

** 52992-0063; 219969; "Evaluation of XDE-750 in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay"; (V.A. Linscombe, M.R. Schisler, D.J. Beuthin; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011037; 7/23/01); Chinese Hamster Ovary (CHO-K₁-BH₄) cells were exposed to XDE-750 (lot no. F0031-143, purity: 94.5%) at concentrations ranging from 31.25 to 2070 ug/ml for 4 hours at 37° C in the first assay and from 250 to 2070 ug/ml in the 2nd assay under conditions of both non-activation and activation with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation

frequency of the 6-thioguanine-resistant colonies. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 2/16/06)

** 52992-0066; 219972; "Evaluation of GF-871 in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay"; (V.A. Linscombe, M.R. Schisler, S.D. Seidel; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 031135; 2/25/04); Chinese Hamster Ovary (CHO-K₁-BH₄) cells were exposed to GF-871 (XDE-750 TIPA (triisopropanolamine)) (lot no. 173-162-1A; a.i.: 41.3%) at concentrations ranging from 250 to 4000 ug/ml (based on the active ingredient) for 4 hours at 37° C under conditions of both non-activation and activation with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation frequency of the 6-thioguanine-resistant colonies. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 2/20/06)

CHROMOSOME EFFECTS

** 52992-0064; 219970; "Evaluation of XDE-750 in an *In Vitro* Chromosomal Aberration Assay Utilizing Rat Lymphocytes"; (V.A. Linscombe, K.M. Jackson, M.R. Schisler, D.J. Beuthin; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011040; 4/25/02); Primary lymphocyte cultures, procured from the whole blood of male Sprague-Dawley rats (stimulated with PHA for 48 hours), were treated with 32.3 to 2070 ug/ml of XDE-750 (lot no. F0031-143, purity: 94.5%) for 4 hours (both non-activation and activation), followed by 20 hours of incubation in Assay A1. In Assay B1, the cells were treated with 125 to 2070 ug/ml of the test material for 24 hours (non-activation) and then harvested or treated with 62.5 to 2070 ug/ml for 4 hours, followed by an incubation of 20 hours (activation) prior to being harvested. In Assay C1, the cells were treated with 400 to 2070 ug/ml for 24 hours and then harvested (non-activation). An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. One hundred metaphases/replicate (200 cells/treatment level) were examined for structural abnormalities. A treatment-related increase in chromosomal aberration was evident under conditions of non-activation. The positive controls were functional. **Possible adverse effect indicated. Study acceptable.** (Moore, 2/17/06)

** 52992-0065; 219971; "Evaluation of GF-871 in an *In Vitro* Chromosomal Aberration Assay Utilizing Rat Lymphocytes"; (V.A. Linscombe, K.M. Jackson, M.R. Schisler; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 031134; 2/27/04); Primary lymphocyte cultures, procured from the whole blood of male Sprague-Dawley rats (stimulated with PHA for 48 hours), were treated with 62.5 to 4000 ug/ml of XDE-750 TIPA (triisopropanolamine) in GF-871 (lot no. 173-162-1A; a.i.: 41.3%) for 4 hours (both non-activation and activation), followed by 20 hours of incubation and with 31.3 to 4000 ug/ml of the active ingredient for 24 hours (non-activation) in Assay A1. In Assay B1, the cells were treated with 62.5 to 4000 ug/ml of the active ingredient for 4 hours (non-activation), followed by 20 hours of incubation and then harvested. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. A treatment-related increase in chromosomal aberration was not evident under either conditions of non-activation or activation. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 2/17/06)

DNA DAMAGE

** 52992-0067; 219977; "Evaluation of XDE-750 in the Mouse Bone Marrow Micronucleus Test"; (P.J. Spencer, T.A. Gorski; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011125; 3/7/02); Six CD-1 mice/sex/group were dosed orally by gavage with 0 (aqueous 0.5% Methocel®), 500, 1000 or 2000 mg/kg/day of XDE-750 (lot no. F0031-143, purity: 94.5%) for 2 consecutive days. Twenty-four hours after the second dose, all of the surviving animals were euthanized. In addition, 6 animals/sex were dosed with 120 mg/kg of cyclophosphamide (positive control) and euthanized at 24 hours post-dose. Bone marrow samples from the femurs of each animal were examined and the percentage of polychromatic erythrocytes (PCE) which were micronucleated was determined in 2000 PCEs per mouse. The percentage of PCE's in the erythrocyte population was calculated as well. There

was no treatment-related increase in the percentage of micronucleated PCEs. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 2/21/06)

** 52992-0068; 219978; "Evaluation of GF-871 in the Mouse Bone Marrow Micronucleus Test"; (P.J. Spencer, V.A. Linscombe, J. Grundy; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 031136; 2/25/04); Six CD-1 mice/sex/group were dosed orally by gavage with 0 (water), 500, 1000 or 2000 mg/kg/day of XDE-750 TIPA (triisopropanolamine) in GF-871 (lot no. 173-162-1A; a.i.: 41.3%) for 2 consecutive days. Twenty-four hours after the second dose, all of the surviving animals were euthanized. In addition, 6 animals/sex were dosed with 120 mg/kg of cyclophosphamide (positive control) and euthanized at 24 hours post-dose. Bone marrow samples from the femurs of each animal were examined and the percentage of polychromatic erythrocytes (PCE) which were micronucleated was determined in 2000 PCEs per mouse. The percentage of PCE's in the erythrocyte population was calculated as well. There was no treatment-related increase in the percentage of micronucleated PCEs. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 2/21/06)

NEUROTOXICITY

Rat Acute Oral Neurotoxicity Study

52992-0041; 219902; "Revised Report for: XDE-750: Acute Neurotoxicity Study in Fischer 344 Rats"; (B.R. Marable, A.K. Andrus, K.E. Stebbins; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011073R; 12/18/01, revised, 1/28/02); Ten Fischer 344 rats/sex/group were dosed orally by gavage with 0, 500, 1000, or 2000 mg/kg of XDE-750 (lot no. F0031-143; purity: 94.5%) (vehicle: aqueous 0.5% Methocel). No deaths resulted from the treatment. The 2000 mg/kg males and females demonstrated an increased incidence of fecal (males) or urine (females) staining in the perineal region during the first 72 hours post-dose. The mean body weight data did not reveal any treatment-related effect. There was no treatment-related effect noted in the FOB or motor activity data. The neuropathological examination did not reveal any treatment-related lesions. **No adverse effect indicated. Rat acute neurotoxicity NOEL:** (M/F) 2000 mg/kg (based upon the lack of effects at the highest dose tested); **Study acceptable.** (Moore, 1/30/06)

Rat Subchronic Neurotoxicity Study

52992-0042; 219903; "XDE-750: Chronic Neurotoxicity Study in Fischer 344 Rats"; (J.P. Maurissen, A.K. Andrus, K.A. Johnson, M.D. Dryzga; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011049N; 9/22/03); Ten Fischer 344 rats/sex/group received 0, 5, 50, 500 or 1000 mg/kg/day of XDE-750 (lot no. F0031-143; purity: 94.5%) in the diet for 12 months. Functional Observational Battery (FOB) and motor activity assessments were performed prior to the initiation of the study and after 1, 3, 6, 9 and 12 months of treatment. There was no treatment-related effect upon the mean body weights of the study animals. The 1000 mg/kg males did demonstrate an increased level of defecation over the course of the study. However, no other parameters in the FOB indicated a possible effect upon the autonomic nervous system. There was no treatment-related effect upon the motor activity assessment. No treatment-related lesions were identified in the neuropathological examination. **No adverse effect indicated. Chronic Neurotoxicity NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of treatment-related neurotoxic effects on the highest dose tested); **Study acceptable.** (Moore, 1/27/06)

RAT METABOLISM

52992-0069; 219979; "[¹⁴C]XDE-750: Absorption, Distribution, Metabolism, and Excretion in Male Fischer 344 Rats"; (J. Liu; ABC Laboratories, Inc., Columbia, MO; Study No. 47456; 9/19/03);

Four male Fischer 344 rats/group were dosed once orally by gavage with 1000 (Group A) or 50 mg/kg (Group B) of [^{14}C]XDE-750 (XDE-750-pyr-2,6- C^{14}) (lot no. F380-135a, radiochemical purity: 98.6%, specific activity: 27.4 mCi/mmol) or for 14 days with 50 mg/kg/day of XDE-750 (lot no. 199902336-15B, purity: 99.5%), followed by a single dose of 50 mg/kg (Group C) of the radiolabeled compound. Urine and fecal samples were collected for up to 168 hours post-dose. The excretion profile was characterized, the distribution of radiolabeling in the tissues at 168 hours post-dose was determined and the isolation and identification of the radiolabeled metabolites was attempted. In the excretion profile, 51 to 62% (urine plus cage wash) and 33 to 43% of the administered dose was recovered in the urine and feces, respectively, for the three groups. The percentage of the administered dose recovered in the first 24 hours post-dose was greatest for Group B (94%), declining to 89% for Group C and 74% for Group A. The urine elimination half lives for the α phase ranged from 2.85 (Group B) to 3.78 hours (Group A). For the β phase, the half lives ranged from 10.23 (Group B) to 12.25 hours (Group C). The skin was the primary tissue site of recovery at 168 hours post-dose. Otherwise, the radiolabeling was well distributed throughout the other tissues and the carcass except for the fat. In the urine, 96% of the administered dose was unmetabolized parent compound. In the feces, 100% of the administered dose was unmetabolized. **Study supplemental** (study did not include a complete evaluation of the absorption profile for the test material). (Moore, 2/23/06)

52992-0070; 219980; "XDE-750, Triisopropanolamine Salt: Dissociation and Metabolism in Male Fischer 344 Rats"; (J.Y. Domoradzki, D.L. Rick, A.J. Clark; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 031129; 2/27/04); Four male Fischer 344 rats/group were dosed orally by gavage with (A) 50 mg/kg of [^{14}C] XDE-750 (XDE-750-pyridine-2,6- ^{14}C) (radiochemical purity: 98.25%, specific activity: 28.6 mCi/mmmole) or (B) 96 mg/kg of [^{14}C] XDE-750 TIPA (triisopropanolamine) which was prepared from [^{14}C] XDE-750-pyridine-2,6- ^{14}C with the appropriate amount of triisopropanolamine. Urine, fecal and plasma samples were collected for up to 120 hours post-dose. In the excretion profile, 42 to 46% (urine plus cage wash) and 51 to 54% of the administered dose was recovered in the urine and feces, respectively, for the two groups. The percentage of the administered dose recovered in the first 24 hours post-dose was 93 to 94%. The percentage of the administered dose recovered in the plasma was limited to 0.04 to 0.05% over the time course of sample collection. The peak plasma levels for both dosing regimens was within the 1st 15 minutes post-dose. The plasma elimination half lives for the α phase were 0.338 and 0.509 hours for the A and B dosing regimens, respectively. For the β phase elimination, the half lives for 8.84 and 13.0 hours for A and B, respectively. The urine elimination half lives for the α phase were 2.84 and 2.54 hours for A and B, respectively. For the β phase, the half lives were 7.81 and 10.7 hours for A and B, respectively. The urinary excretion rates for XDE-750 demonstrated that a molar equivalent of the active ingredient had been administered in both dosing regimens. In the metabolic profile, all of the radiolabel in the urine was unmetabolized parent compound in Group A and 99.2% in Group B. In the feces, only the unmetabolized parent compound was detectable in both dosing regimens. **Study supplemental.** (Moore, 2/28/06)

Note: These study data provide a complete characterization of the absorption, excretion and metabolism of the active ingredient. Although a biliary excretion study was not performed despite the high percentage of the administered dose recovered in the feces, analysis of the radiolabel in the plasma in this study revealed only a limited percentage of the administered dose being recovered in the blood over the time course of the study (0.04 to 0.05%). These data indicate that the recovery of radiolabel in the urine was likely a reasonable assessment of the percentage of administered dose which had been absorbed.

SUBCHRONIC TOXICITY STUDIES

Rat 4-Week Dietary Toxicity Study

52992-0050; 219936; "XDE-750: 4-Week Repeated Dose Dietary Toxicity Study in Fischer 344 Rats"; (K.E. Stebbins, S.J. Day; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 001031; 8/8/00); Five Fischer 344 rats/sex/group received 0, 10, 100, 500 or 1000 mg/kg/day of XDE-750 (lot no. F-0031-125; purity: 95.4%) in the diet for 4 weeks. No deaths resulted from the treatment. The mean body weights and food consumption were not affected by the treatment regimen. No treatment-related effect was noted in the ophthalmology, hematology, clinical chemistry, or urinalysis examinations. There was no treatment-related effect on the mean absolute or relative organ weights. In the gross necropsy examination, all of the animals in the 1000 mg/kg group and three males and two females in the 500 mg/kg group had enlarged cecums. The histopathological examination did not reveal any treatment-related lesions. **No adverse effect indicated. 4-Week Dietary NOEL:** (M/F) 100 mg/kg/day (based upon the incidence of enlarged cecums for both sexes in the 500 mg/kg group); **Study supplemental** (non-guideline study). (Moore, 12/23/05)

Rat Subchronic Dietary Toxicity Study

52992-0046; 219907; "Revised Report for XDE-750: 13-Week Dietary Toxicity Study with 4-Week Recovery in Fischer 344 Rats"; (M.D. Dryzga, K.E. Stebbins; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 001221; 5/17/01, revised, 8/29/01); Ten Fischer 344 rats/sex/group received 0, 10, 100, 500, or 1000 mg/kg/day of XDE-750; lot no. F0031-143; purity: 94.5% in the diet for 13 weeks. Additional ten animals/sex each received 0 or 1000 mg/kg/day of the test material for 13 weeks and then were maintained for another 4 weeks on control feed as recovery groups. No deaths resulted from the treatment. The mean body weights or food consumption were not affected by the treatment. The ophthalmology, hematology, clinical chemistry or urinalysis examinations did not reveal any treatment-related lesions. The mean absolute and relative full cecum weights of both sexes in the 500 and 1000 mg/kg groups were greater than those values for the control in the main study ($p < 0.05$). The mean absolute and relative empty cecum weights for the males in the 500 mg/kg group and for both sexes in the 1000 mg/kg group were greater than those values for the controls ($p < 0.05$). In the recovery groups, the mean absolute and relative full and empty cecum weights of both sexes in the 1000 mg/kg group were greater than the control values ($p < 0.05$). In the gross pathology, there was an incidence of enlarged cecum in both sexes of the 1000 mg/kg group in both the main study and the recovery (main study: (M/F) 0: 0/10 vs. 1000: 10/10, recovery: (M/F) 0: 0/10 vs. 1000: 2/10). In the histopathology examination, very slight diffuse hyperplasia of the cecal epithelium was noted in all of the 1000 mg/kg males in the main study. This effect was not evident in the females of the main study or the males in the recovery group. **No adverse effect indicated. Subchronic Dietary NOEL:** (M/F) 100 mg/kg/day (based upon the increased absolute and relative weight of the cecum in both sexes of the 500 mg/kg/day treatment group); **Study acceptable.** (Moore, 12/23/05)

52992-0044; 219905; "XDE-750: A 13-Week Dietary Reproduction Probe in CD Rats"; (A.B. Liberacki, M.S. Marty, J. Thomas; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011046; 12/12/01); Ten CD rats/sex/group received 0, 100, 500 or 1000 mg/kg/day of XDE-750 (lot no. F0031-143, purity: 94.5%) in the diet for 13 weeks. The mean body weights of both sexes in the 1000 mg/kg group were less than those of the controls (NS). There was no apparent effect upon food consumption. The hematology, clinical chemistry, urinalysis, and ophthalmology evaluations were not performed. In the gross necropsy, the size of the cecum was increased for animals of both sexes in the 500 and 1000 mg/kg groups ((M): 0: 0/10 vs. 500: 5/10, 1000: 8/9, (F) 0: 0/10 vs. 500: 5/10, 1000: 8/10). The mean absolute and relative cecum weights, both full and empty, were greater for both sexes in the 500 and 1000 mg/kg groups than for the controls ($p < 0.05$). In the histopathological examination, very slight epithelial hyperplasia in the crypt cells of the cecum was noted for both sexes in the 1000 mg/kg group ((M/F) 0: 0/10 vs. 1000: 9/10). Very slight epithelial hyperplasia in the crypt cells of the ileum was evident for the males of the 1000 mg/kg group (0: 1/10 vs. 1000: 8/10). **No adverse effect indicated. Reported Subchronic Dietary NOEL:** (M/F) 100 mg/kg/day (based upon greater absolute and relative size of the cecum in the 500 mg/kg treatment group); **Study supplemental.** (Moore, 12/30/05)

52992-0047; 219908; "GF-871: 90-Day Dietary Toxicity Study in Fischer 344 Rats"; (K.E. Stebbins, M.D. Dryzga; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 031140; 2/25/04); Ten Fischer 344 rats/sex/group received 0, 465, 1211 or 2421 mg/kg/day of GF-871 (XDE-750 triisopropanol ammonium, lot no. 173-162-1A, a.i.: 41.3% (triisopropanol ammonium salt)) in the diet for 13 weeks. No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption. The hematology, clinical chemistry, urinalysis and ophthalmology did not reveal any treatment-related effects. In the gross necropsy, an enlarged cecum was noted for all of the 2421 mg/kg group animals. The mean absolute and relative full cecum weights of both sexes in the 1211 and 2421 mg/kg groups were greater than those of the control ($p < 0.05$). The mean absolute and relative empty cecum weights of the 2421 mg/kg males were greater than that of the control ($p < 0.05$). No lesions were evident in the histopathological evaluation. **No adverse effect indicated. Subchronic Dietary NOEL (formulated product):** (M/F) 465 mg/kg/day (based upon increased cecum weights of both sexes in the 1211 mg/kg group); **Study acceptable.** (Moore, 12/29/05)

Rat 28-Day Repeated Dosing Dermal Toxicity Study

52992-0051; 219937; "XDE-750: 28-Day Dermal Toxicity Study in Fischer 344 Rats"; (K.E. Stebbins, J. Thomas, S.J. Day; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 011219; 12/23/02); The skin of 10 Fischer 344 rats/sex/group was exposed to 0, 100, 500 or 1000 mg/kg/day of XDE-750 (lot no. F0031-143; purity: 94.5%) for 6 hours/day, 7 days/week for 4 weeks under a semi-occluded wrap. The test material was suspended in an aqueous 0.5% methylcellulose preparation. No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption of the study animals. The ophthalmology, hematology, clinical chemistry and urinalysis did not reveal any treatment-related effects. In the necropsy examination, the mean absolute and relative full cecum weights of the 100 and 500 mg/kg males were greater than those values for the controls ($p < 0.05$). However, there was not a good dose-response relationship for this parameter and no effect was noted for the empty cecum. There skin at the treatment site of the 500 and 1000 mg/kg males exhibited a greater response to the treatment than the control animals with 2 and 3 animals demonstrating slight epidermal hyperplasia for these groups, respectively in contrast to none of the control males. **No adverse effect indicated. Systemic NOEL:** (M/F) 1000 mg/kg (based on the lack of treatment-related effects at the highest dose tested); **Dermal NOEL:** (M) 100 mg/kg (based upon epidermal hyperplasia), (F) 1000 mg/kg (based upon the lack of a treatment-related effect at the highest treatment level); **Study acceptable.** (Moore, 1/31/06)

Dog 4-Week Dietary Toxicity Study

52992-0045; 219906; "XDE-750: A 4-Week Dietary Toxicity Study in Beagle Dogs"; (K.E. Stebbins, P.C. Baker; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 001030; 10/4/00); Two beagle dogs/sex/group received 0, 1500, 4500 or 15000 ppm of XDE-750 (lot no. F-0031-125, purity: 95.4%) in the diet for 4 weeks ((M) 0, 61.5, 192.6, 542.8 mg/kg/day, (F) 0, 62.1, 177.2, 556.0 mg/kg/day). No deaths resulted from the treatment. There was no apparent treatment-related effect upon body weight gain. The 15000 ppm males demonstrated a lower mean food consumption over the last three weeks of the study.

No treatment-related effects were noted in the hematology, clinical chemistry, urinalysis, ophthalmology, necropsy or histopathology data. **No adverse effect indicated. 4-Week Dietary NOEL:** (M) 4500 ppm (192.6 mg/kg/day) (based upon lower mean feed consumption for the two males in the 15000 ppm group); (F) 15000 ppm (556.0 mg/kg/day) (based upon the lack of treatment-related effects in the 15000 ppm group); **Study supplemental.** (Moore, 12/27/05)

Dog Subchronic Dietary Toxicity Study

52992-0048; 219909; "Revised Report for: XDE-750: 13-Week Dietary Toxicity Study in Beagle Dogs"; (K.E. Stebbins, P.C. Baker; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; 12/20/01, revised, 2/6/02); Four beagle dogs/sex/group

received 0, 1500, 7500 or 30000 ppm of XDE-750 (lot no. F-0031-143, purity: 94.5%) in the diet for 13 weeks ((M) 0, 54.5, 282, 1070 mg/kg/day, (F) 0, 52.7, 232, 929 mg/kg/day). No deaths resulted from the treatment. There was no apparent treatment-related effect upon food consumption. The hematology, clinical chemistry, ophthalmology, and urinalysis did not reveal any treatment-related effects. The mean absolute and relative liver weights of both sexes in the 30000 ppm group were greater than the values for the controls ($p < 0.05$). In the histopathological examination, the stomachs of the animals in the 30000 ppm group exhibited slight cellular hyperplasia and hypertrophy ((M) 0: 0/4 vs. 30000: 4/4, (F) 0: 0/4 vs. 30000: 4/4). **No adverse effect indicated. Subchronic Dietary NOEL:** (M/F) 7500 ppm ((M): 282 mg/kg/day, (F): 232 mg/kg/day) (based upon the cellular hyperplasia noted in the stomachs of both sexes in the 30000 ppm group); **Study acceptable.** (Moore, 1/13/06)

Mouse 4-Week Dietary Toxicity Study

52992-0049; 219910; "XDE-750: A 4-Week Repeated Dose Dietary Toxicity Study in CD-1 Mice"; (B.L. Yano, M.D. Dryzga; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 001048; 8/2/00); Five CD-1 mice/sex/group received 0, 10, 100, 500 or 1000 mg/kg/day of XDE-750 (lot no. F-0031-125, purity: 95.4%) in the diet for 4 weeks (calculated a.i. uptake: (M) 0, 11.0, 102.0, 524.7, 1038.0 mg/kg/day; (F) 0, 10.8, 105.0, 530.4, 1058.0 mg/kg/day). No deaths resulted from the treatment. There was no treatment-related effect upon food consumption. The hematology, clinical chemistry or ophthalmology evaluations did not reveal any treatment-related effects. The necropsy examination did not reveal any treatment-related lesions or effects upon organ weights. In the histopathology examination, there was an increased incidence of decreased glycogen in the liver of the 1000 mg/kg males (0: 0/5 vs. 10: 1/5, 100: 1/5, 500: 0/5, 1000: 2/5). There also was an incidence of hepatocytic hypertrophy (0: 0/5 vs. 1000: 2/5). **No adverse effect indicated. 4-Week Dietary NOEL:** (M) 500 mg/kg/day (based upon the incidence of decreased glycogen and the hepatocytic hypertrophy in the livers of the 1000 mg/kg/day males); (F) 1000 mg/kg/day (based upon the lack of treatment-related effects at the highest dose level); **Study supplemental.** (Moore, 12/28/05)

Mouse Subchronic Dietary Toxicity Study

52992-0043; 219904; "XDE-750: A 13-Week Dietary Toxicity Study in CD-1 Mice"; (K.E. Stebbins, S.J. Day, J. Thomas; Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI; Study ID. 001240; 12/20/01); Ten CD-1 mice/sex/group received 0, 10, 100, 500 or 1000 mg/kg/day of XDE-750 (lot no. F0031-143, purity: 94.5%) in the diet for 13 weeks. No deaths resulted from the treatment. There were no treatment-related effects on the mean body weights or food consumption. The hematology, clinical chemistry and ophthalmological evaluations did not reveal any treatment-related effects. There was no treatment-related effect upon the mean organ weights. The histopathological examination did not reveal any treatment-related lesions. **No adverse effect indicated. Subchronic Dietary Toxicity NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of a treatment-related effect at the highest dose administered); **Study acceptable.** (Moore, 12/22/05)